REMARKS/ARGUMENTS

Claims 1-84 are pending in the instant application. Claims 1 and 82 have been amended. No new matter has been added.

I. The Rejections under 35 U.S.C. § 101

Claims 1-84 stand rejected for allegedly directing to non-statutory subject matter. Citing *In re Bilski*, the Examiner asserts that the instant method 1) is not tied to a particular machine or apparatus and 2) does not transform a particular article into a different state or thing. With regard to Applicants' previous amendment, the Examiner asserts that "the ultimate step of storing a score on computer readable media is considered an inconsequential post solution activity." (Page 3 of the instant Office Action)

Without acquiescing to the Examiner's assertions, and merely to expedite prosecution of the instant application, Applicants herewith provide amendments to the first step recited in claims 1 and 82 which now reads, "providing at least one *de novo* sequence from mass spectrometry data of sequences of fragments of said macromolecule to a computer-based system that implements the identification of sequences of molecules and sequence modifications from mass spectrometry data". Support for this amendment can be found throughout the specification as filed, and specifically at least at paragraph [0042] and originally filed claim 88, as well as paragraphs 0043 and 0080. Accordingly, since Claims 1-84 are believed to be directed to statutory subject matter, Applicants respectfully request withdrawal of the present rejection.

II. The Rejections under 35 U.S.C. §103(a)

Claims 1-12 and 63-84 stand rejected under §103(a) as being unpatentable over Dancik *et al.* (Journal of Computational Biology, 1999, volume 6, pp. 327-342) in view of Pevzner *et al.* (Genome Research, 2001, volume 11, pp. 290-299).

Applicants respectfully disagree and traverse the rejection.

Assuming that it would be proper to combine the references, Applicants maintain that such a combination would not reach the present invention.

The Examiner asserts that Pevzner et al is relied upon for teaching methods drawn to efficient database searching for identification of mutated and modified protein via mass spectrometry." (Page 13 of the instant Office Action)

Applicants submit that while Pevzner may teach methods for identifying mutated and modified proteins via mass spectrometry, Pevzner does not teach or suggest a method incorporating a step for the identification and characterization of particular modifications, using a modification catalog or otherwise, but instead teach a mutation/modification –"tolerant" method that "reliably identifies peptides differing by up to two mutations/modifications from a peptide database." (Page 290, Abstract). That is, they are able to identify peptide matches in a database in spite of the presence of a mutation/modification in a peptide.

The Examiner asserts that Pevzner further teaches the use of a spectral alignment approach as a filter in a new database search algorithm that reliably identifies peptides differing by up to two mutations/modifications from a peptide in a database." (Page 13 of the instant Office Action)

Applicants reiterate that the Pevzner "spectral alignment" technique involves matching ion series in MS/MS spectra to peptide sequences without using a stringent parent ion mass filter. By contrast, the instant method incorporates interpreting mass differences between a de novo sequence and a sequence in a sequence database identified by mass-match alignment. In addition, the Pevzner approach comes with a tradeoff in the accuracy of its scoring function that often assigns high scores to incorrect peptide identification by chance (page 298, column 1, paragraph 2), thereby limiting its application in high-throughput environments, such as described in the instant specification. Applicants further submit that Pevzner does not teach a modification catalog of any kind, let alone for interpreting mass differences between a de novo sequence and a sequence in a sequence database identified by mass-match alignment.

The Examiner asserts that the listings of a plurality of modified peptides used in the disclosed methods (see Figure 1 and Table 1 of Pevzner et al.) read on the use of a modification catalog to identify sequence modification as instantly claimed. (Page 13 of the instant Office Action)

Applicants submit that the listings of peptides in Figures 1 and Table 1 of Pevzner are merely provided as examples to illustrate the result of their method. It is important to note that Pevzner does not teach or suggest that either of these listings are to be used in their spectral alignment approach as a modification catalog, nor do they teach utilizing the listings of peptides in Figures 1 and Table 1 to interpret mass differences between a de novo sequence and a sequence in a sequence database identified by mass-match alignment. Indeed, there is no doubt that the Examiner has used the disclosure of the present application to pick and choose selected portions of Pevzner et al., any listing of peptides, in an attempt to recreate the claimed invention. Applicants respectfully submit that the Examiner's conclusion is based upon an improper hindsight reconstruction of the claimed invention, which, instead of looking at the prior art as a whole, picks and chooses teachings that appears to support a finding of obviousness, while completely disregarding others.

Figure 1 of Pevzner is a theoretical spectra of peptides intended to demonstrate their "Shared Peaks Count" method. In fact, in the disclosure of this method, Pevzner teach away from identifying and/or cataloging the molecular mass of a modification as in the instant application. As stated in the 2nd paragraph of column 2 on page 292, Pevzner *et al* teach, "For the sake of simplicity, we represent a spectrum S as a set of integers, corresponding to masses of fragment ions and ignore the intensities of the fragment ions." Furthermore, at the end of the same paragraph, Pevzner teaches "SPC [Shared Peaks Count] is, of course, an intuitive measure of spectral similarity. However, this measure diminishes very quickly as the number of mutations increases thus leading to limitations in detecting similarities in MS/MS database search." The peptides listed in Table 1 of Pevzner *et al* are merely an accounting of the sample peptides matched against the yeast protein database using their disclosed algorithms. This table does not provide information for interpreting mass differences between a de novo sequence and a sequence in a sequence database identified by mass-match alignment.

The Examiner asserts that "[n]either the instant claims nor the instant specification provide a limiting definition for the contents of 'a modification catalogue'

that would exclude the listings of a plurality modified peptides as taught by Pevnzer et al." (Page 13 of the instant Office Action)

Applicants respectfully disagree and point out that the instant specification discloses adequate description of a modification catalog as used in the instant invention. For example, paragraphs 0029-0032 and 0043-0045 of the instant specification disclose that "mass differences of modification sites between the sequence in the sequence database and the de novo sequence that have been identified by the mass-based alignment are interpreted as modifications identified in a modification catalog." Further, Claim 42 discloses, "wherein said modification information includes at least one of, molecular mass of the modification, specific fragments where the modification occurs, a frequency of occurrence of the modification at those fragments, wherein the frequency of occurrence is the estimated frequency in nature or a frequency as a sample preparation artifact, a mass object for the modification, which represents the additional mass of the modification to the *de novo* sequence at those fragments, the name of the modification, and a modification score for the modification." Claim 43 further discloses, "wherein a modification is selected from, an in vivo or in vitro protein, a peptide modification, and an amino acid substitution." Paragraph 0046 goes on to state "In one embodiment of the present invention, mass-based alignment of de novo sequences are utilized to accurately identify sequence variations and post-translational protein modifications, thus allowing for these types of searches to succeed in a high-throughput environment."

Applicants reiterate that Pevzner does not teach a modification catalog of any kind, let alone for interpreting mass differences between a de novo sequence and a sequence in a sequence database identified by mass-match alignment. As stated above, Pevzner *et al.* do not teach the identification and characterization of any modifications, using a modification catalog or otherwise, but instead teach a mutation/modification –"tolerant" method that "reliably identifies peptides differing by up to two mutations/modifications from a peptide database." (Page 290, Abstract). As disclosed in the instant specification, the sequence homology approach used by the prior art can only consider a small number of specific isobaric equivalences. By

contrast, Example 5 of the instant specification demonstrates that the methods and systems of the present invention were able to identify 12 sites of single amino acid variance in amniotic fluid lactotransferrin.

As demonstrated in Example 3 of the instant specification, the methods and systems of the present invention allows low abundance proteins with poor coverage to be found, even if proteins with higher coverage dwarf them. Further, this approach can find short, isobaric equivalences of an arbitrary residue length, in this case, three consecutive residues or masses, within a given mass tolerance (paragraph 0056 of the instant specification). However, Pevzner acknowledge that while their method places correct peptides among the 500 top-scoring peptides in most cases, spectra of very short peptides and low quality spectra are an exception. (page 299, 1st paragraph of column 1).

Finally, as demonstrated in Example 6 of the instant specification, the methods and systems of the present invention allowed the identification of six different types of modifications in a human lens crystalline sample. By contrast, Pevzner teaches that "a number of questions related to modification-tolerant MS/MS database searches remain open." (page 299, 3rd paragraph,column 1). Moreover, Pevzner discloses that their method does not rely on a prior knowledge of possible types of modifications. (page 294, 3rd paragraph of column 2).

The Examiner assert that "Applicants reliance of exemplary embodiments from the specification fail to demonstrate how the language of the instant claims differentiates the claimed invention from that of set forth in the prior art." (Page 15 of the instant Office Action).

Without acquiescing to the Examiner's assertions, and merely to expedite prosecution of the instant application, Applicants submit herewith an amendment to independent Claims 1 and 82, which now recite the following limitation:

> (c) interpreting mass differences between a sequence in the sequence database and the at least one *de novo* sequence using a modification catalog, said mass differences having been identified within said mass-based alignment,

wherein said modification catalog contains information for accurately identifying sequence variations and post-translational protein modifications,

Support for the present amendment can be found at least at Paragraph [0046] of the instant specification and claim 42 as originally filed. Not only does Pevzner not teach the use of a modification catalog, it also teaches away from the ability to identify post-translational modifications.

Accordingly, the instant claims are not obvious over Dancik *et al.* in view of Pevzner *et al.* and Pevzner *et al* repeatedly teach away from the present invention. Thus, Applicants respectfully request withdrawal of the present rejection.

The Examiner has rejected Claims 1-27 and 63-84 under §103(a) as allegedly being unpatentable over Dancik *et al.* in view of Pevzner *et al.* and further in view of Mann *et al.* (Analytical Chemistry, 1994, volume 66, pp. 4390-4399).

As discussed above, and in the previously filed Response of July 2, 2007, Dancik *et al.* in view of Pevzner *et al.* do not disclose each and every limitation of Claims 1 or 82, nor those claims dependent thereupon, for at least the reasons given above. Mann *et al.* do not cure the deficiencies of Dancik *et al.* in view of Pevzner *et al.*, as Mann *et al.* do not teach methods for: 1) interpreting mass differences between the sequence in the sequence database and the *de novo* sequence using a modification catalog, said mass differences having been identified within said mass-based alignment, or 2) grouping identifications of sequences in the sequence database from at least one *de novo* sequence into an identified macromolecule list that agrees with the *de novo* sequencing results.

The Examiner has rejected Claims 1-84 under §103(a) as being unpatentable over Dancik *et al.* in view of Pevzner *et al.* in view of Mann *et al.* and further in view of Bader (Bioinformatics, 2003, volume 19, pp. 1869-1874).

As discussed above, and in the previously filed Response of July 2, 2007, Dancik *et al.* in view of Pevzner *et al.* and further in view of Mann *et al.* do not disclose each and every limitation of Claim 1 and 82 or those claims dependent thereupon. Bader *et*

al. do not cure the deficiencies of Dancik *et al.*, Pevzner *et al.* and Mann *et al*, as Bader *et al.* do not teach a method for identifying a macromolecule having a sequence and sequence modifications thereof from mass spectrometry data following the steps recited in the claims of the instant application.

Accordingly, the instant claims are not obvious over the above-cited references Thus, Applicants respectfully request withdrawal of the present rejection.

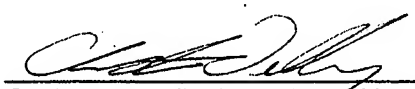
CONCLUSION

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Please charge any fees, including fees for extension of time, or credit overpayment to Deposit Account No. **50-4634**, referencing **Attorney's Docket No. 123888-182131 (PTX-0003)**.

Respectfully submitted,

Date: May 14, 2009

By: 
Christopher De Vry (Reg. No. 61,425)

Goodwin|Procter LLP
135 Commonwealth Drive
Menlo Park, CA 94025
Tel. No.: (650) 752-3100
Fax No.: (650) 853-1038